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Synthesis of Polysubstituted 4-Fluoroquinolinones

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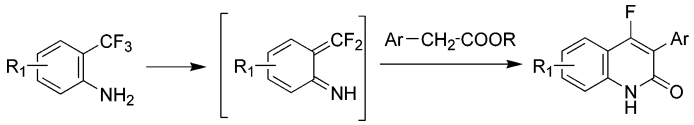
ABSTRACT



A convenient one-pot synthesis of 4-fluoroquinolinones that are active against KDR kinase is described. The mechanism of the reaction is believed to involve the formation of a quinone methide intermediate.

Quinolinones belong to a chemical class that possesses biological activity depending on the specific substitution within the molecule.[1] The lactam functionality of a quinolinone moiety may be engaged in hydrogen bond donor−acceptor interactions similar to ones observed for ATP molecules as well as for various kinase inhibitors.[2] Our goal was to explore the preparation of 4-fluoro-substituted quinolinones and, thus, to address the introduction of fluorine into the critical portion of this molecular motif. The fluorine atom is often used to block in vivo metabolism at particular molecular sites. Although the sites of oxidative metabolism for quinolinone-containing small molecules may vary, the introduction of a fluorine atom into specific and not easily accessible positions remains a challenging task for organic chemists working on medicinal projects.

It has been shown that the anionically activated trifluoromethyl group has great utility in the synthesis of various aromatic, heteroaromatic, and aliphatic compounds.[3] These include syntheses of 2-(substituted 1-alkenyl) anilines,[4] 2-substituted benzothiazoles and benzoxazoles,[5] 4(5)-dihydro-1*H*-imidazole,[6] triazines,[7] and isoxazoles,[7] 1,3-disubstituted naphthalenes,[8] 2,4-di- or 2,3,4-trisubstituted quinolines,[9] 7-(substituted amino)-5,6-dihydrobenz[*c*]acridines,[10] 3-aryl-4-aminocinnolines,[11] and fused fluoronaphthalenes[12] and the recently reported synthesis of polysubstituted naphthalenes.[13] It has been suggested that all of the above transformations proceed via the initial proton abstraction from the anilinic nitrogen to afford the quinone methide intermediate **Q** (Scheme 1). The subsequent reaction of this intermediate with various nucleophiles leads to the array of products observed.

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(12) Kiselyov, A. S.; Strekowski, L. *Tetrahedron Lett.* **1994**, *35*, 7597.
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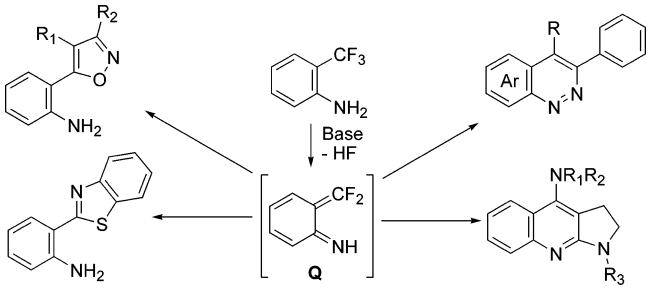
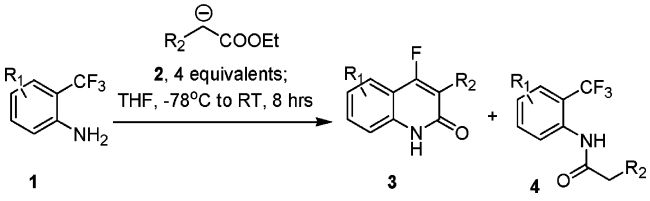
Scheme 1. Transformations of Quinone Methide Intermediate



In this paper we report a facile synthesis of 4-fluorinated quinolinones via the condensation of (2-trifluoromethyl) aniline with esters of arylacetic acids under basic conditions (Scheme 2). To optimize the yield of **3** and to turn this

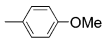
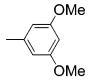
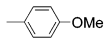
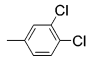
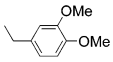
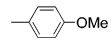
Scheme 2



methodology into a successful synthetic tool we studied the effects of several factors on the outcome of this reaction, including (i) reaction temperature, (ii) the ratio of substrate **1** to base, (iii) reaction time, (iv) solvent, and (v) nature of base. Temperature was found to have a profound effect on the reaction course. For example, treatment of **1** with 1 equiv of **2** (generated from the corresponding ester of arylacetic acid and LDA) in THF at −78 °C for 24 h followed by the aqueous quench of the reaction mixture with water yielded only starting material **1**. Similar treatment of **1** at −30 °C (MeCN/ethylene glycol/dry ice mixture) for 8 h allowed the isolation of **3** in 22% yield along with starting material **1** (69%).

Notably, further increase in the reaction temperature to 0 °C and room-temperature did not affect the yield of **3**. The optimal empirically found ratio of **1** to base was 1:6; lower ratios resulted in lower yields of **3**, whereas higher ratios (6−12) did not significantly affect the reaction outcome. THF as well as dimethoxyethane (DME) were efficacious solvents for the reaction (31−66% yields of **3**); the reactions conducted in diethyl ether afforded only 12−20% yield of **3**. Several amide bases, including LDA, LiTMP (2,2,6,6-tetramethylpiperidide), and LiHMDS (1,1,1,3,3,3-hexamethyldisilazide) furnished essentially similar yields of **3**. The nature of the cation did not affect the outcome of this reaction. The reaction times of 4−5 h were essential to ensure the complete conversion of **1** to **3** at ambient temperature.[12] Various amounts of **4** (11−52%) were detected in the reaction mixture; the highest yields of **4** were observed when the reactions were conducted with anions derived from esters of arylacetic acids. The desired product **3** was easily separated by column chromatography. The reaction results for selected examples are listed in Table 1.

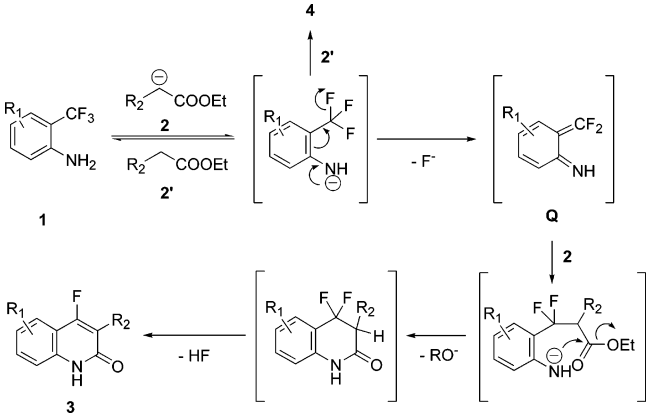
Table 1. Selected Examples for the Preparation of 4-Fluoroquinolinone Derivatives

entry	R_1	R_2	yield of **3** and (**4**), %[a]	entry	R_1	R_2	yield of **3** and (**4**), %[a]
3a	H		66 (11)	3k	5-F		78 (8)
3b	H		59 (13)	3l	5-F		74 (12)
3c	H		71 (8)	3m	5-F		52 (15)
3d	H		63 (14)	3n	8-F		57 (19)
3e	H		58 (17)	3o	8-F		79 (6)
3f	H		72 (7)	3p	8-F		77 (10)
3g	H		52 (21)	3r	5-Br		63 (12)
3h	H		74 (10)	3q	5-Br		55 (18)
3i	5-F		72 (8)	3s	5-Br		61 (16)
3j	5-F		77 (9)	3t	5-Br		81 (11)

[a] Yields refer to isolated analytically pure compounds.

The reported observations can be rationalized by the mechanism presented below (Scheme 3).

Scheme 3. Suggested Mechanism for 4-Fluoroquinolinone Formation



The initial step involves reversible deprotonation of **1** to form the corresponding anion, which is stable at temperatures below −30 °C. At higher temperatures, it undergoes slow elimination of HF to form the quinone methyde intermediate

Q. This active species reacts with **2** to afford condensation product **3** after a series of addition/elimination steps. Alternatively, anilide−anion reacts with the excess of **2′** to afford **4**. Formation of a similar quinone methyde intermediate was suggested in several relevant transformations of (2-trifluoromethyl)aniline.[3]

In summary, we have described a protocol for a rapid assembly of 4-fluoroquinolinones from 2-(trifluoromethyl)-aniline and arylacetic acids. The proposed reaction mechanism for this process involves the formation of the quinone methide as an intermediate. Detailed mechanistic studies of this reaction are in progress in our lab. The selected quinolinone class representatives exhibited activity against KDR tyrosine kinase.

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Supporting Information Available: General experimental procedure and structural characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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